

From the Department of Surgery
University of Basle, Switzerland
Head of Dept.: Prof. Dr. R. Nissen
Research under the direction of P.-D. Dr. W. Hess

The Pharmacological Effect of so-called Morphine Antagonists on the Sphincter of Oddi

**Manometric Studies
with Daptazole and Lorfan**

Inaugural-Dissertation

submitted to the Faculty of Medicine of Basle University
for the purpose of attaining the
doctorate in Medicine

by

Elliot O. Lipchik

from New York (U.S.A.)

1958

Printed by Friedrich Reinhardt AG., Basle

1959

I wish to express my sincere gratitude to P.-D. Dr. W. Hess, whose kind help and cooperation made this work possible. I would also like to thank Dr. A. Celio and Dr. E. Yasargil for their invaluable assistance.

Genehmigt auf Antrag von Herrn Prof. Dr. *R. Nissen*.

Tag der Promotion: 11. Juni 1958.

INTRODUCTION.

Morphine relieves the pain of biliary colic via its central analgesic action, but tends to aggravate this condition by its spasmodic action on the biliary duct system and sphincter of Oddi (1, 2).

Walters and his coworkers (3), were one of the first to show directly this spasmodic effect on the sphincter of Oddi. They showed that 10 mg. morphine sulfate caused a marked increase in the biliary pressure, which began from 2½ to 5 minutes after the injection of the morphine and reached its maximum in fifteen minutes. The pressure may remain two hours or longer.

Higher doses, though still maintaining the spasm, may give better relief from pain by further depressing the higher nerve centers (4). However, this brings on the greater danger of respiratory depression.

Another disadvantage of morphine on the gall bladder system might occur with patients who have impaired liver function. For example, 300 mm H₂O is equivalent to the secretory pressure of the liver (5). A morphine induced spasm of the sphincter of Oddi may raise the pressure in the duct system considerably above this value and thus increase the danger of liver damage.

An anti-spasmodic which could be used in conjunction with morphine, and which would consistently relax the sphincter of Oddi, would be an efficient means of relief for patients with biliary colic. «It might also prevent further extension of the pathologic process (in the duct system) by permitting free drainage of the biliary tract» (4).

Many anti-spasmodics have been tried. *Butsch* and his coworkers (5) showed that Atropin (.0009 gm.) led to dilatation of the pupils and dryness of the mouth but did not relax the sphincter of Oddi spasm caused by morphine. Inhalation of amyl nitrite brought quick improvement but the pressure immediately rose again (5). Glyceryl trinitrate, 0.6 mg. sublingual, caused a more prolonged «but less marked and less rapid decrease in intrabiliary pressure» (5). 240 mg. theophyllineethylenediamine showed the same results (5). Barbiturates have no distinct effect (6). Curare type drugs cause definite decrease of tonus but only when administered in large doses (4 mg./kg.) which cause respiratory paralysis (6). MgSO₄, NaSO₄, MgCl₂, Adrenalin, Histamine, HCl, all have been tried and found wanting (6). Propantheline bromide, an anti-cholinergic, successfully relieved the spasm of the sphinc-



ter of Oddi (8). It later proved to have a rather evanescent action, and quite often had no effect at all (9). Papaverine is seemingly too weak in action (6).

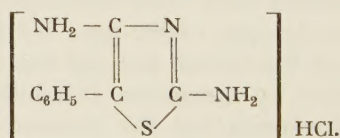
Certain criteria can be developed out of the failures of the above compounds for an effective anti-morphine (anti-spasmodic) drug. It must be specific in its action, i.e., have no antianalgesic action. It must act promptly and consistently, and last at least as long as the morphine effect. To meet these demands much work has been done in the last few years on the so-called morphine antagonists. For example, *Schapiro* and *Beal* (9), in 1953, showed that N-allylnormorphine produced a prompt decrease in common duct pressure. However, N-allylnormorphine is an antagonist of morphine which abolishes all the morphine effects including its analgesic powers, while also abolishing effectively the sphincter of Oddi spasm (10). It is itself somewhat toxic and some of the clinical results obtained with it are of conflicting nature.

It is the purpose of this paper to show the results of two relatively new morphine «antagonists»—

2:4-diamino-5-phenylthiazole
(Amiphenazole; Daptazole)
and
3-Hydroxy-N-allyl-morphinantartrat
(Laevallorphan; Lorfan)

on the motility of the sphincter of Oddi after morphine induced spasm was caused.

2:4-diamino-5-phenylthiazole HCl, hereafter referred to as Daptazole, is a colorless crystalline compound, first synthesized in 1950, by *W. Davies*, in the Department of Chemistry of Melbourne University (11), and has the structural formula of



It is readily soluble in water at room temperature, but decomposes on standing. Its pharmacology has been investigated by *Shaw* and *Bentley* (12, 13) and *Shaw* and *Shulman* (14) and *McKeogh* and *Shaw* (15).

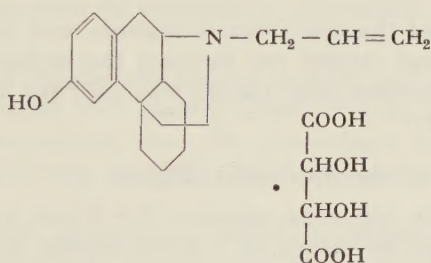
They showed its antagonistic effects on morphine induced respiratory depression. Alone, it may act as a non-specific respiratory stimulant resembling caffeine and nikethamide in its action (16), as well as having a direct peripheral action on the muscles

involved in the respiration of the cat (17). It also has a slight parasympathomimetic effect (13).

Intravenous doses of up to 300 mg. have been given to healthy volunteers and produced few subjective symptoms, as well as no changes in blood pressure, heart rate, respiration, EEG (19). However, *Shulman* and *Trethewie* (17) stated that very high dosages appear to have a markedly depressant effect on both respiration and blood pressure, which may result in death.

In a series of experiments on four dogs, *Mercier* (18) found no consistent antagonistic effect on the sphincter of Oddi spasm caused by morphine. Up to this present date there has been no published data on Lorfan's antagonistic effect on the morphine induced spasm of the sphincter of Oddi.

3-Hydroxy-N-allyl-morphinantartrat (Laevallorphan or Lorfan, as it shall hereafter be referred to), a slightly acid substance, easily soluble in water and insoluble in lipoid solvents, is analogous with Dromoran (3-Hydroxy-N-methyl-morphinantartrat or Laevorphan) from which it is only differentiated by the substitution of N-methyl by an N-allyl group. All the antagonistic activity resides in its levorotatory isomer (21). Its structural formula is:



Lorfan has little action by itself (in the dog) but antagonizes both the central and peripheral effects of Laevorphan (22). It neutralizes the inhibitory action on respiration of about one hundred fold larger doses of morphine and morphine like drugs. However, it also neutralizes the analgesic action, but only with much higher doses (20, 23).

Zindler and *Ganz* (20) showed no distinct side effects or phenomena resulting from small overdosages. It can be administered subcutaneously, intramuscularly, or intravenously. Slight side effects of unspecific nature, like nausea, vomiting, dizziness, numbness, tiredness, sleepiness, occur very rarely in unanesthetized patients.

Usually a dosis of Lorfan corresponding to 1/50 of the amount of morphine prescribed, suffices for the elimination of the de-

pressant effects which morphine has on the respiratory system. However, rather higher doses of the "antagonist" are necessary to eliminate other undesirable effects of morphine. The use of more than 1 mg. per 10 mg. morphine is not recommended by the manufacturer.

There has been no experimental work published dealing with Lorfan's effect on the spasm of the sphincter of Oddi caused by morphine.

MATERIALS AND METHODS.

Our experiments were done on ten in-patients from the Department of Surgery of the University of Basle, Switzerland. Included in our examination are also a series of experiments on three dogs. All of the patients were admitted to the hospital because of gall bladder disease, with surgical indications. In all the patients, operative cholangiography and manometry were performed at the time of the operation. Only those patients whose sphincter of Oddi function was shown to be radiomanometrically normal were used. Seven of the ten patients underwent cholecystectomy ; two patients underwent cholecystostomy; one had a choledochostomy performed.

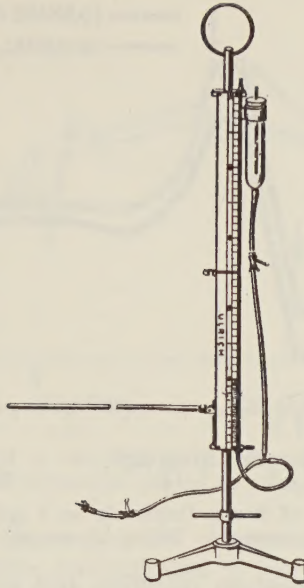
At the time of the operation, a cannula was inserted into the common duct and carried out through the incision. A perfusion apparatus, as modeled after Caroli, was used for all the measurements (Figure 1).

Description of the Apparatus (Figure 1).

The perfusion apparatus consists of a T-bar which can be attached to a table by means of a screw-clamp, and a glass tube with a manometric scale from 0-50 c.c. The 0-point of the manometer can be adjusted to the height of the gall duct. A moveable sliding carriage is attached to the side of the T-bar; and a glass vessel capable of holding 150 c.c. hangs therein. This fluid container, with physiologic NaCl for our experiments, is connected with the cannula leading into the gall duct. The manometer is attached to the tube leading to the cannula by means of a T-shaped glass piece in a horizontal connection. The fluid container is closed on top with a rubber plug, which has a built-in glass tube. This tube dips into the fluid and emits air bubbles, clearly indicating fluid out-flow into the gall duct.

Technique.

The 0-point of the manometer is adjusted to the height of the gall duct (midpoint between the anterior and posterior abdominal



UE 1710

Fig. 1. Perfusion apparatus for manometrical examinations of the gall ducts as modeled after J. Caroli.

wall). The screw-clamps are opened and the gall ducts are filled. The vessel is raised very slowly, centimeter by centimeter, and the pressure determined when the physiologic saline just flows through the sphincter of Oddi. This pressure is the *perfusion pressure*.

After each such perfusion pressure determination, the *residual pressure* is measured by clamping the tubing between manometer and the vessel containing the saline.

The pressure should then drop somewhat and stabilize itself. This residual pressure corresponds to the tonus of the sphincter, that is, to the equilibrium between the fluid in the gall duct and the tonus of the sphincter. Upon contraction of the Oddi sphincter the pressures rise, and, of course, upon dilation they fall. After determining the patients' perfusion and residual pressures, the drugs were injected and their results tested by measuring the pressures approximately every three minutes. All the injections were made intravenously.

In four of the patients (cases 1, 2, 3, 4) we injected morphine, waited for the contraction, and then injected Daptazole.

In another four patients (cases 5, 6, 7, 8) we injected morphine, waited for the contraction, and then injected Lorfan.

The action of Lorfan only was tested in one patient (case 10),

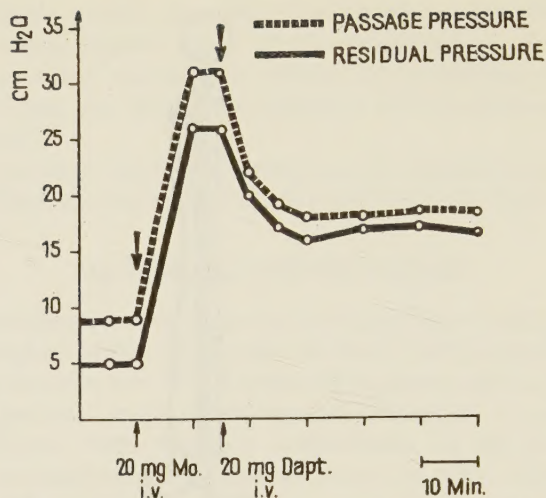


Fig. 2. Case 1. The effect of 20 mg. Daptazole on a sphincter of Oddi contraction caused by 20 mg. of morphine.

as well as the simultaneous injection and action of Lorfan and morphine on two patients (cases 9 and 10).

The series of experiments with the dogs were done in almost the same manner. The action of morphine, Daptazole, and Lorfan, respectively, was recorded; as well as Daptazole and Lorfan's effect on the spasm of the sphincter of Oddi caused by morphine.

RESULTS.

I. Patients.

Case 1. E. H., white, female, 55 years old, 62 kg., 5th post operative day (cholecystectomy) (Fig. 2).

The base values of 9 cm. water passage pressure and 5 cm. water residual pressure (hereafter referred to simply as passage pressure over residual pressure, e.g., 9/5) was increased to 31/26 on the injection of 20 mg. morphine within ten minutes. Daptazole (20 mg.) was injected intravenously fifteen minutes after the morphine injection. An immediate relaxation was noted, the pressure falling to 22/20 within five minutes, and to 18/16 within fifteen minutes, where it remained for another twenty-five minutes at which time we stopped recording.

Case 2. M. S., white, female, 50 years old, 51 kg., 10th post operative day (cholecystostomy) (Fig. 3).

From the base values of 9/5.5 the pressure rose to 19/17.5 within fifteen minutes after the injection of 10 mg. morphine. Upon

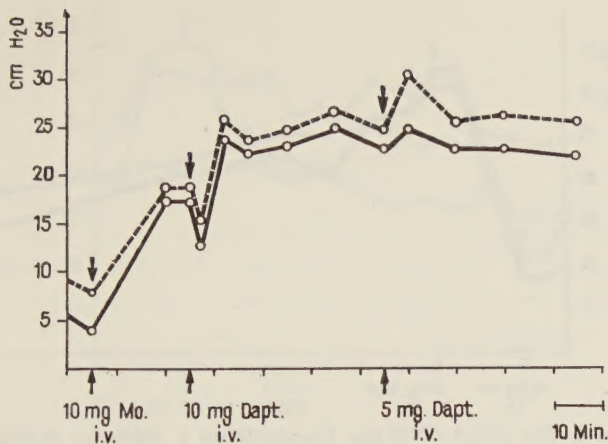


Fig. 3. Case 2. The action of two injections of Daptazole on the sphincter of Oddi contraction caused by morphine.

injection of 10 mg. Daptazole, the pressures fell immediately to 15.5/13. However, after five minutes it rose again to 22/21. We waited forty minutes with approximately the same readings and injected 5 mg. more of Daptazole, whereupon the pressures rose to 31/25, but returned again to 26/23 in fifteen minutes.

Case 3. R. B., white, female, 24 years old, 65 kg., 19th post operative day (cholecystectomy) (Fig. 4).

Upon 10 mg. morphine injection the pressures rose from 15/13 to 29/27 within ten minutes. Fifteen minutes after the morphine, we injected 10 mg. Daptazole. The pressures fell close to the base values (16/14.5) within ten minutes and stayed low for almost two hours.

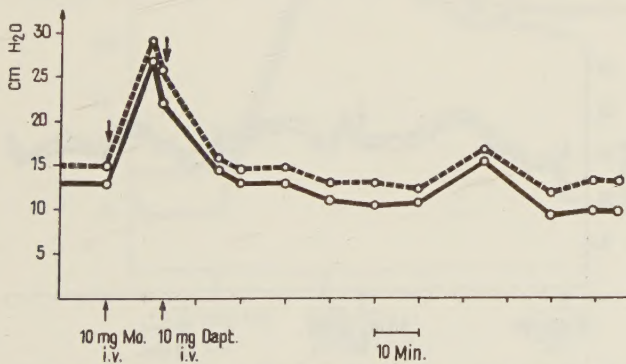


Fig. 4. Case 3. The effect of 10 mg. Daptazole on a sphincter of Oddi spasm caused by 10 mg. morphine.

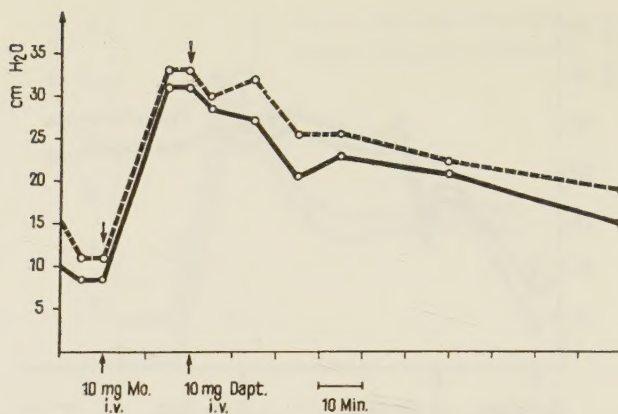


Fig. 5. Case 4. The effect of 10 mg. Daptazole on a sphincter spasm induced by 10 mg. morphine.

Case 4. L. S., white, female, 44 years old, 50 kg., 7th post operative day (cholecystectomy) (Fig. 5).

After the injection of 10 mg. morphine, the pressures rose from 11/8.5 to 33/31. We then injected 10 mg. Daptazole. The pressures fell slowly to 25.5/20.5 within twenty minutes, and did not approach the base value until two hours later.

Case 5. H. F., white, female, 43 years old, 65 kg. (cholodochostomy) (Fig. 6).

The sphincter of Oddi reacted rather slowly to 10 mg. morphine as it rose to 20.5/19.5 from the base values of 12/10 after twenty-three minutes. After waiting forty-five minutes, 0.5 mg. Lorfan was injected. The pressure rose from 17.5/16.5 to 20/19, but fell within six minutes close to the former reading of 17/16, where it stayed for well over an hour.

Case 6. W. M., white, male, 30 years old, 71 kg., 18th post operative day (cholecystectomy) (Fig. 7).

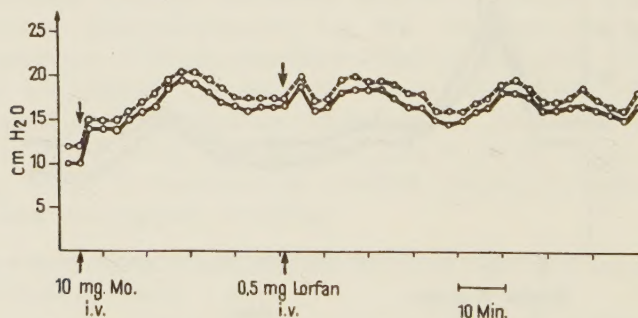


Fig. 6. Case 5. The effect of 10 mg. morphine and 0.5 mg. Lorfan on the sphincter of Oddi.

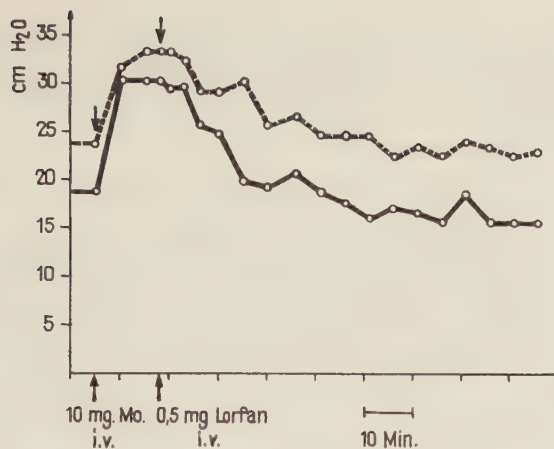


Fig. 7. Case 6. The effect of 0.5 mg. Lorfam on the spasm of the sphincter of Oddi caused by 10 mg. morphine.

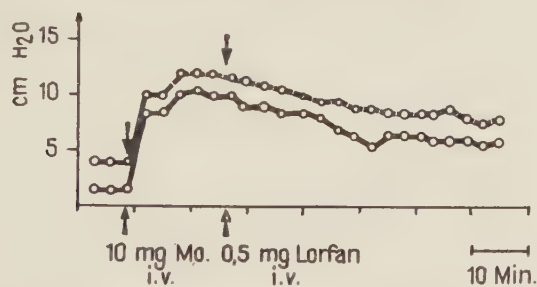


Fig. 8. Case 7. The effect of 0.5 mg. Lorfam on the spasm of the sphincter of Oddi caused by 10 mg. morphine.

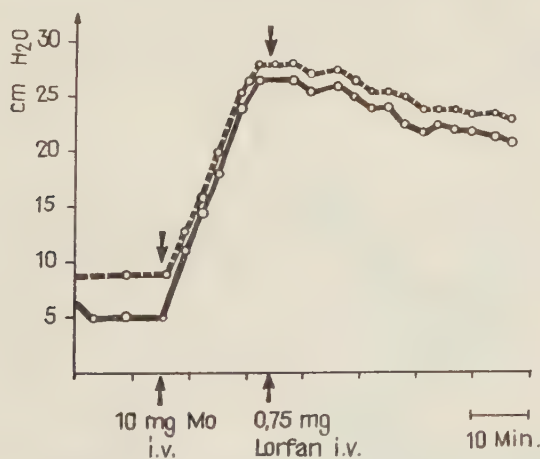


Fig. 9. Case 8. The effect of 0.75 mg. Lorfam upon the contraction of the sphincter of Oddi caused by 10 mg. morphine.

The pressures rose from 24/19 to 33.5/30.5 after 10 mg. morphine within ten minutes. After 0.5 mg. Lorfam injection at that height, the pressures fell steadily but slowly to 26.9/19.5 within twenty minutes.

Case 7. H. H., white, male, 45 years old, 54 kg., 10th post operative day (cholecystectomy) (Fig. 8).

The pressures rose from 4/1.5 to 10/8.5 within three minutes after the injection of 10 mg. morphine. 0.5 mg. Lorfam was injected about eighteen minutes later at pressures of 11.5/10. The pressures descended very slowly until they reached the value of 8/6 after about fifty minutes.

Case 8. O. B., white, female, 57 years old, 50 kg., 40th post operative day (choledochostomy) (Fig. 9).

After the injection of 10 mg. morphine, the pressures rose from the base value of 9/5 to 28/26.5 within twenty minutes. At this level Lorfam 0.75 mg. was injected. The pressures fell slowly, but after forty-five minutes were still high at 23/21.

Case 9. H. S., white, female, 29 years old, 75 kg., 11th post operative day (cholecystectomy) (Fig. 10).

10 mg. morphine and 0.5 mg. Lorfam were injected simultaneously. The pressures rose from 6.5/4 to 15/14 within ten minutes. This approximate level was maintained for almost fifty minutes.

Case 10. M. E., white, female, 32 years old, 54 kg., 5th post operative day (cholecystectomy) (Figs. 11 a and b).

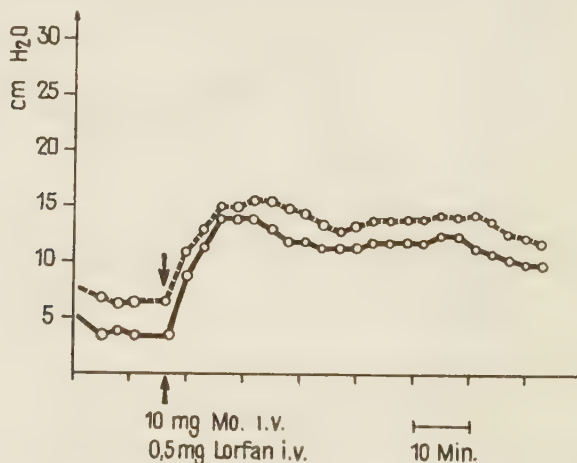


Fig. 10. Case 9. The effect of a combined injection of 10 mg. morphine and 0.5 mg. Lorfam on the sphincter of Oddi.

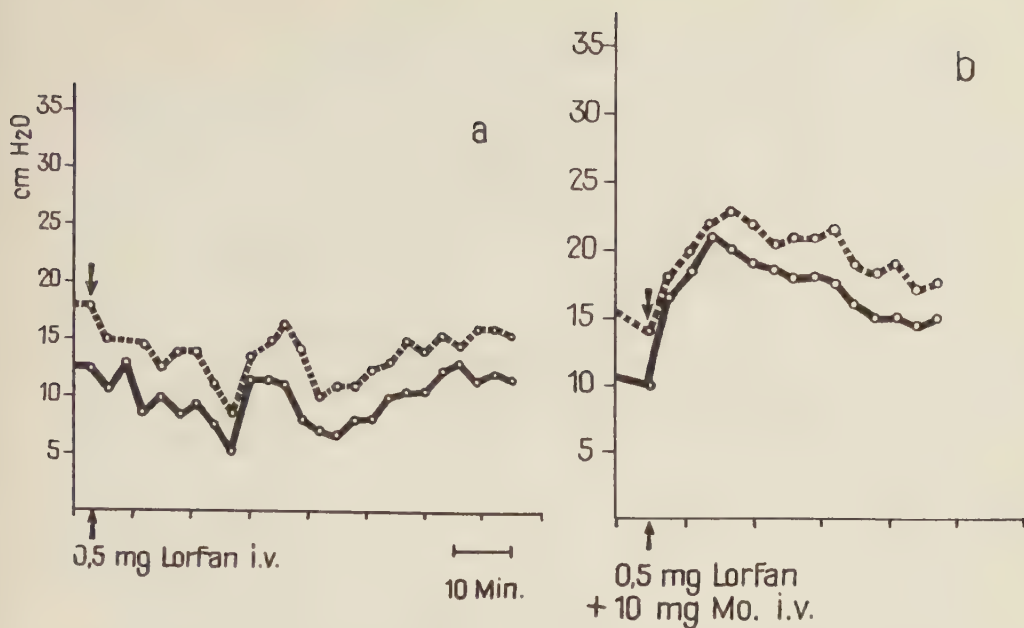


Fig. 11. Case 10.

a. The effect of 0.5 mg. Lorfan on the sphincter of Oddi.

b. The effect of a combined injection of 0.5 mg. Lorfan and 10 mg. morphine.

The effect of Lorfan alone was recorded. 0.5 mg. was injected after determining the base values of 18/12.5. The pressures fell to a low of 8.5/5.0 within twenty-five minutes, but rose again sharply.

On another day a combination of 0.5 mg. Lorfan and 10 mg. morphine was injected. The pressures rose from 14/10 to 23/20 within twelve minutes. After forty minutes they were recorded at 17.5/15.

II. Dogs.

Case 1. 16 kg. male dog (Figs. 12 a, b, and c).

The base value was established to be 6/3. After the injection of 12 mg. morphine the pressure rose to 22.5/21 within six minutes. However, it fell rather quickly to 9/5 within fifteen minutes after the morphine injection. When the pressures returned to 8/3.5, approximating the base values (6/3), we injected 12 mg. Daptazole. A small rise in pressure to 12/8 occurred within three minutes, but fell again to 7/4.5 within fifteen minutes after the injection (Figure 12 a).

On another day, 12 mg. morphine were injected. After a spasm occurred, Lorfan (0.5 mg.) was injected. Thirteen minutes after

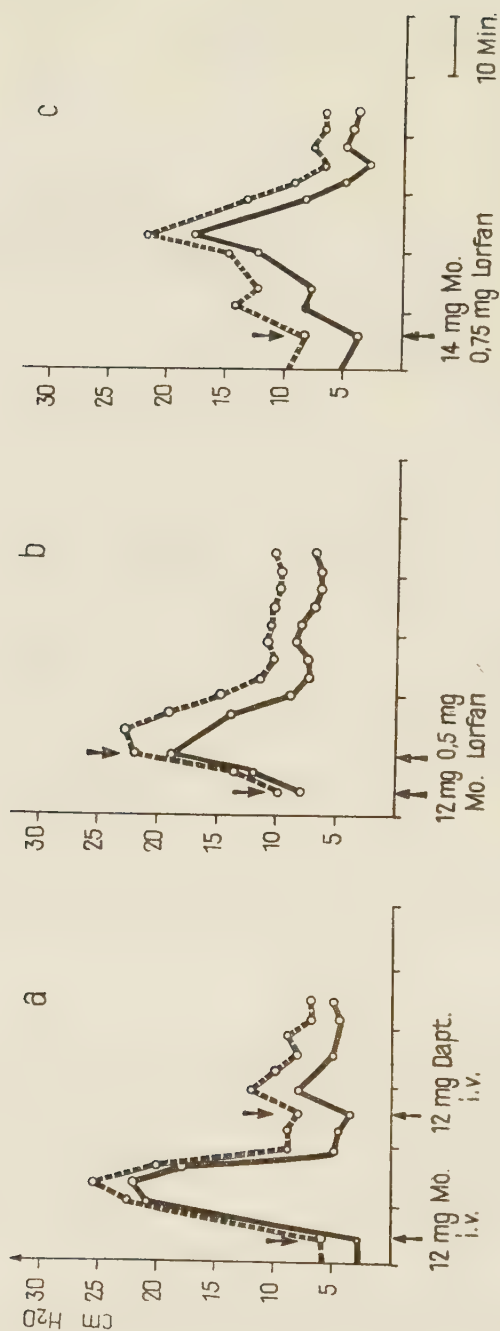


Fig. 12. Dog case 1.

- The individual effect of 12 mg. morphine and 12 mg. Daptazole on the sphincter of Oddi.
- The effect of 0.5 mg. Lorf. on the spasm of the sphincter of Oddi caused by 12 mg. morphine.
- The action of a combined injection of 14 mg. morphine and 0.75 mg. Lorf.



Fig. 13. Dog case 2.

- a. The effect of 16 mg. morphine on the sphincter of Oddi.
- b. The effect of 0.75 mg. Lorfane on the sphincter.
- c. The effect of a combined injection of 0.75 mg. Lorfane and 16 mg. morphine on the sphincter of Oddi.

the second injection the pressures were down to 11/7.5, which approximated the base pressures of 10/8 (Figure 12b).

On another occasion a combination of 14 mg. morphine and 0.75 mg. Lorfane were injected after the base pressures of 8.5/4.0 were established. The dog vomited during the slowly proceeding injection. The pressures rose to 12.5/8.0 within seven minutes after the injection, and to 22/18 within sixteen minutes. The pressures then fell to approximately the base values of 9.5/5.0 within twenty-five minutes (Figure 12c).

Case 2. 14 kg. male dog (Figs. 13a, b, and c).

First, the action of 16 mg. morphine alone was recorded. After the injection the pressures rose from 13/9 to 33/28.5 within twelve minutes. Within twenty minutes the pressures returned to their base values (Figure 13a).

At another time the effect of 0.75 mg. Lorfane was recorded. After nine minutes the pressures had risen from 23/19 to 31/26, but returned to 22/17 eighteen minutes after the injection (Figure 13b).

Finally, 16 mg. morphine and 0.75 mg. Lorfane were injected together. Within seven minutes after the injection the pressures rose from 15/10 to 31/29. They remained at approximately this level for six minutes and then descended to 17.5/12.5 after a further span of fifteen minutes (Figure 13c).

Case 3. 14.5 kg. male dog (Figs. 14a, b, and c).

The effects of Lorfane, Daptazole, and a combination of morphine and Lorfane were measured.

0.75 mg. Lorfane caused an increase of pressure from 13/8 to 17.5/11.5. Within fifteen minutes after the injection the pressures had returned to their base values (Figure 14a).

On another occasion 15 mg. Daptazole caused an immediate but transient rise of six minutes from 15/11.5 to 19/14.5 (Figure 14b).

At a later date 16 mg. morphine together with 0.75 mg. Lorfane caused a rise in pressure from 12.5/8.5 to 23/22 within six minutes. The pressures returned to about their original base values after fifteen minutes (Figure 14c).

DISCUSSION.

A. Daptazole.

Patients.

Cases 1 and 3 exhibited an immediate fall in pressure after the Daptazole injection. However, only case 3 had a total relaxation,

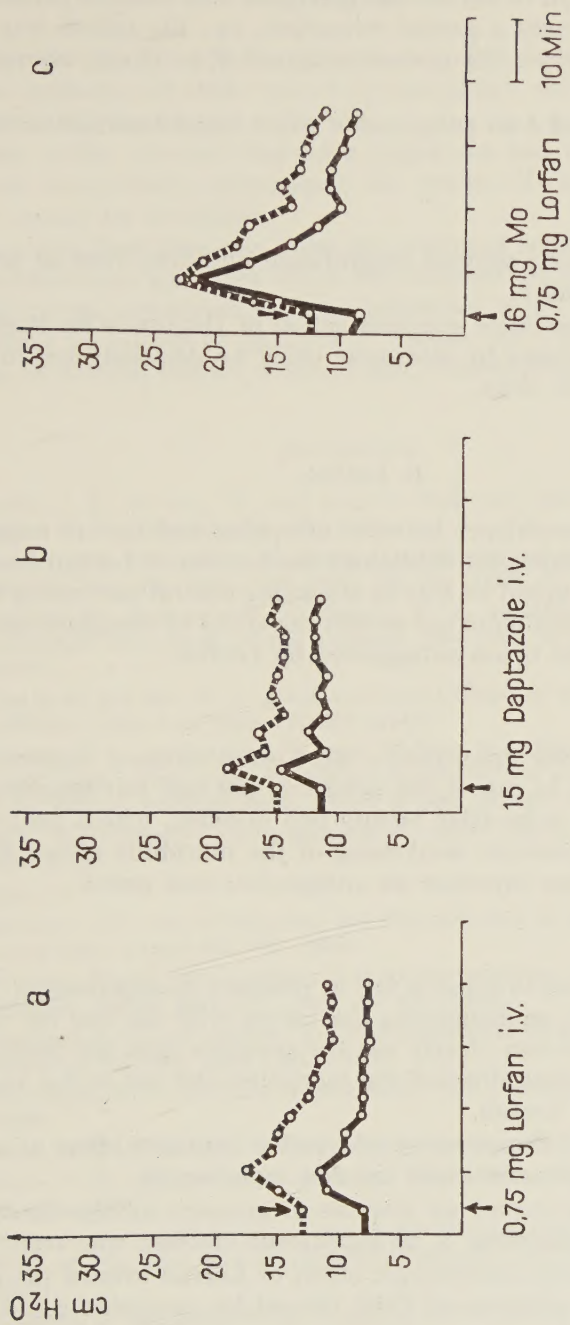


Fig. 14. Dog case 3.

a. The effect of 0.75 mg. Lorfam on the sphincter of Oddi.

b. The effect of 15 mg. Daptazole on the sphincter.

c. The effect of a combined injection of 16 mg. morphine and 0.75 mg. Lorfam on the sphincter.

i.e., a quick return to the normal perfusion and residual pressures. Case 1 showed only a partial relaxation, i.e., the spasm was not lifted entirely, since the pressures stayed 9 to 11 cm. above the base values.

In cases 2 and 4 no antagonistic effect toward morphine could be noted.

Dogs.

Daptazole alone showed insignificant and brief rises of pressure in cases 1 and 3.

Thus, no specific or constant action of Daptazole by itself or on the spasm caused by morphine could be demonstrated in the patients or in the dogs.

B. Lorfan.

Chemical resemblance between morphine and Lorfan suggested a possible competitive inhibitory mechanism of Lorfan toward morphine. This might be true in morphine central nervous system activity, but according to our results the effect of morphine on the sphincter of Oddi is not antagonized by Lorfan.

Patients.

In none of our experiments did Lorfan cause a noteworthy fall in pressure. In case 6, the pressures did fall, but approached the base values only after twenty-two minutes, which probably indicated a physiologic weakening of the morphine effect. Even with simultaneous injection no antagonism was noted.

Dogs.

Lorfan seemed to cause a fall in pressure in experiments 1, 2, and 3. However, on comparing the curves with the one for morphine alone, one can clearly see the pressure falls are probably due to the transient effect of the morphine and not to the antagonistic effect of Lorfan.

As mentioned above, we noted a rather transient effect of morphine on the sphincter in all the dog experiments.

Lorfan alone caused an increase in pressure in experiment 2. However, in experiment 3, no significant increase was seen.

Thus, a specific antagonistic effect of Lorfan toward the contraction of the sphincter of Oddi caused by morphine could not be demonstrated.

Summary.

The antagonistic effect of Daptazole and Lorfan on the spasm of the sphincter of Oddi caused by morphine, was tested on ten patients and three dogs.

Our results showed that both Daptazole and Lorfan had no distinct antagonistic effect upon the spasm of the sphincter of Oddi caused by morphine.

It seems that they also have no consistent action on the choleodochoduodenal sphincter when administered alone.

Therefore, whenever a contraindication exists for the use of morphine in biliary or pancreatic disease, the addition of Daptazole or Lorfan cannot suspend this contraindication.

References.

1. Smith, J. L., Walters, W., and Beal, J.: Study of Choledochal Sphincter Action. *Gastroenterology* 20, 129 (1952).
2. Curreri, A. R. and Gale, J. W.: Effect of Analgesics and Anti-Spasmodics on Common Duct Pressures. *Ann. Surg.* 132, 348 (1930).
3. Walters, W., McGowan, J. M., Butsch, W. L., and Knepper, P. A.: The Pathologic Physiology of the Common Bile Duct. *J. Am. Ass.* 109, 20 (1937).
4. Best, R. R. and Barr, H. J.: Administration of Morphine and Antispasmodics in Biliary Colic. *Ann. Surg.* 117, 207 (1943).
5. Butsch, W. L., McGowan, J. M., and Walters, W.: Clinical Studies on the Influence of Certain Drugs in Relation to Biliary Pain and to the Variation in Intrabiliary Pressure. *Surg., Gynec. & Obst.* 63, 451 (1936).
6. Hess, W.: «Operative Cholangiographie», Georg Thieme Verlag, Stuttgart 1955, p. 29.
7. Ibid. p. 5.
8. Sangster, A. J.: Use of Morphine and Propantheline in Intravenous Cholecystography. *Lancet* 269, 525 (1955).
9. Schapiro, H. and Beal, J.: Effect of N-allylnormorphine on the Choledochal Sphincter Action. *Surg. (St. Louis)* 34, 870 (1953).
10. Goodman, L. A. and Gillman, A.: "Pharmacological Basis of Therapeutics", Macmillan Co., New York 1955, p. 229.
11. Rosenblum, E. I.: Conquest of Intolerable Pain. *Austral. J. Pharm.* 37, 116 (1956).
12. Shaw, F. H. and Bentley, C.: Morphine Antagonism. *Nature* 169, 712 (1952).
13. Shaw, F. H. and Bentley, C.: Morphine Antagonism. *Austral. J. Exp. Biol.* 33, 143 (1955).
14. Shaw, F. H. and Shulman, A.: Treatment of Intractable Pain with Large Doses of Morphine and Diaminophenylthiazole. *Brit. Med. J.* 4926, 1367 (1955).
15. McKeogh, J. and Shaw, F. H.: Morphine and Amiphenazole in Intractable Pain. *J. Pharm. Pharmacol.* 5, 357 (1956).

16. *Shulman, A.*: Letters to the Editor. *Lancet* 269, 1394 (1955).
 17. *Shulman, A. and Trethewie, E. R.*: Effect of Amiphenazole on Respiration and Blood Pressure of the Decerebrate Cat. *Austral. J. Exp. Biol.* 34, 315 (1956).
 18. Personal Communication.
 19. *Shaw, F. H.*: Letters to the Editor. *Lancet* 269, 774 (1955).
 20. *Zindler, M. and Ganz, P.*: Ein Antidot der Opiate. *Dtsch. Med. Wschr.* 12, 440 (1955).
 21. *Landmesser, C. M., Formel, P. F., and Converse, G. J.*: Comparative effects of a new narcotic antagonist upon the respiratory responses to carbon dioxide during narcotic and barbiturate depression in anaesthetized man. *Anaesthesiology* 16, 520 (1955).
 22. *Schallek, W. and Walz, D.*: Cardiovascular and Central Nervous System Effects of Morphinan Series. *Proc. Soc. Exp. Biol.* 87, 233 (1954).
 23. *Fromherz, R. and Pellmont, B.*: Morphine Antagonisten. *Experientia* 8, 394 (1952).
-